


Chronic Cough in Children

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Educational Objectives

- Understand and describe current cough guidelines
- Describe pitfalls in cough management
- Describe practical and cost-effective ways to manage chronic cough
- Apply and interpret common tests used to evaluate patients with chronic cough

Conflict of Interest

- Principal investigator for Cerecor-investigating new medication for chronic cough in adults.

**Chronic Cough in Children
is a Multi-Disciplinary Symptom**

- Pediatrician
- Allergy/Immunology
- Pulmonary
- Otolaryngology
- Gastroenterology
- Speech therapy
- Behavior counseling
- Psychiatrist

Cough in Children

- Normal, protective defensive mechanism, necessary for effective airway clearance

Cough in Children

- Normal, protective defensive mechanism, necessary for effective airway clearance
AND
- Common symptom of respiratory disease

Cough in Children

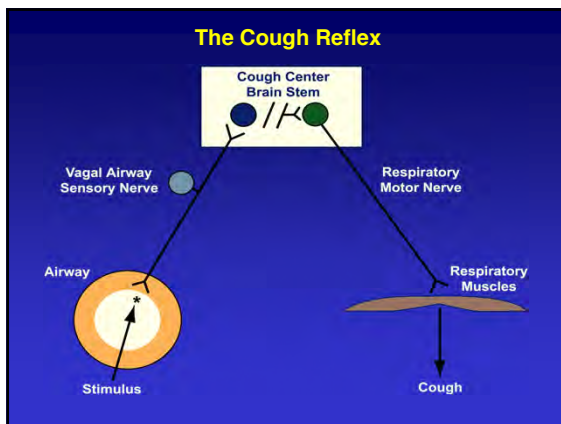
- Important protective defensive mechanism, necessary for effective airway clearance
AND
- Common symptom of respiratory disease
- Most common symptom for visit to MD office in US (3.4%)
Cherry, Natl Ambulatory Medical Care Survey 2007
- < 16 y/o (1° care) cough with RTI lasts 20 days
Moore, Br J Gen Pract 2008
- Parents report cough-22% preschool children w/out URI
-10% school-age children w/out URI
Doell, Thomas 1996; Layr, BMJ 1993
- Parental reporting of cough correlates poorly w/ objective measures (frequency, duration, intensity) Chang, Arch Dis Child 2003
- Cough known to cause anxiety and depression in parents
Chang, Arch Dis Child 2003; Marchant, Chest 2008

Traditional Recognizable Cough Characteristics in Children

Cough Characteristic	Suggested Underlying Etiology
Barking or brassy cough	Croup, tracheomalacia, habit/psychogenic
Honking or throat-clearing	Habit/psychogenic
Spasmodic/paroxysmal (with or without whoop)	Pertussis-like syndrome
Dry, staccato	Chlamydia in infants

modified from Chang AB, Cough 2005

The Cough Reflex



Anatomy of the Afferent Limb of the Cough Reflex

Irwin, R. S. et. al. Ann Intern Med 2001;134:809-814

↑ CRS vs. Airway Hyperreactivity (AHR)

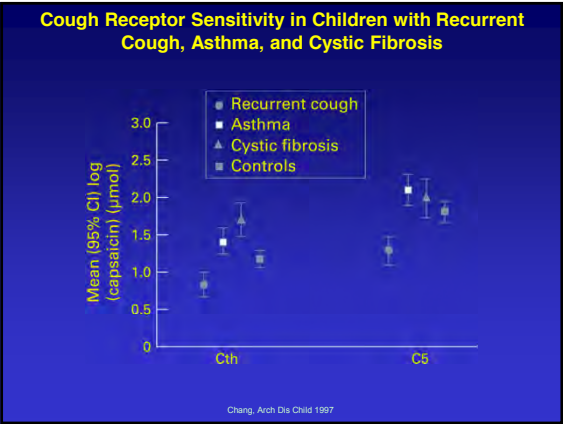
- ↑ CRS and AHR are independent physiologic responses
- ↑ CRS and AHR often co-exist
- ICS→↓ AHR; no Δ CRS
- Inhibition Studies
 - Meds that affect bronchoconstriction (albuterol, atropine, cromolyn) reduce AHR, not CRS
 - Meds that affect CRS (lidocaine, oral codeine) have no effect on bronchoconstriction or AHR

Chang, MJA 2006; 184:398-403
Choudry, ERJ 1990; 3:579-83
Sheppard, ARRD 1983; 127:691-4

Cough Receptor Sensitivity in Acute Asthma

- 31 children with asthma, mean age 9 yrs; hosp w/ acute asthma
- Capsaicin test in hosp, 7-10 d, 4-6 wk
- Results- Some patients cough, some do not; no correlation CRS with FEV1

Chang, Thorax 1997



Classification of Cough

ADULT

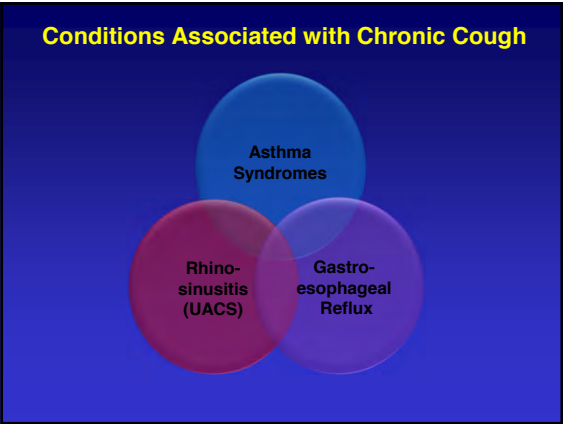
- Acute Cough- up to 3 weeks
- Sub-Acute Cough- 3 to 8 weeks
- Chronic Cough- > 8 weeks

ACCP Guidelines 2006

CHILDREN < 14 yrs

- Acute Cough- up to 4 weeks
- Chronic Cough- > 4 weeks

ACCP Guidelines 2006



Etiology of Chronic Cough	
	Irwin 1990 (n=102)
PNDS/UACS	41%
Asthma	24%
GERD	21%
Bronchiectasis	4%
Chronic Bronchitis/ COPD	3%
Post Infectious	-
Big 3	86%
Multiple causes	26%
Dx made/improved	99%

Etiology of Chronic Cough		
	Irwin 1990 (n=102)	Kastelik 2005 (n=131)
PNDS/UACS	41%	6%
Asthma	24%	24%
GERD	21%	22%
Bronchiectasis	4%	8%
Chronic Bronchitis/ COPD	3%	5%
Post Infectious	-	8%
Big 3	86%	52%
Multiple causes	26%	8%
Dx made/improved	99%	93%

Etiology of Chronic Cough			
	Irwin 1990 (n=102)	Kastelik 2005 (n=131)	Marchant 2006 (n=108)
PNDS/UACS	41%	6%	3%
Asthma	24%	24%	4%
GERD	21%	22%	3%
Bronchiectasis	4%	8%	6%
Chronic Bronchitis/ COPD	3%	5%	PBB 40%
Post Infectious	-	8%	NR 22%
Big 3	86%	52%	9%
Multiple causes	26%	8%	-
Dx made/improved	99%	93%	91%

Chronic Cough in Children

- Prospective, cohort study to evaluate algorithmic approach to dx and tx
- All children (<18 y/o) with chronic cough >3 weeks consecutively referred to Respiratory Clinic at Royal Children's Hospital-Brisbane (6/02-7/04)
- Exclusions --<37-week premie
--known lung disease, neurodevelopmental abnormality, cardiac abnormality

Marchant, Chest 2006

Chronic Cough in Children

- 108 children enrolled (57 female)
- Median age 2.6 years
- Median duration of cough 6 months
- 62% onset in first in 1st year
- Wet cough 89%
- Households with ETS 43%
- Pre-study diagnosis - asthma 50%, no dx 32%,
bronchitis 2%

Marchant, Chest 2006

Chronic Cough in Children

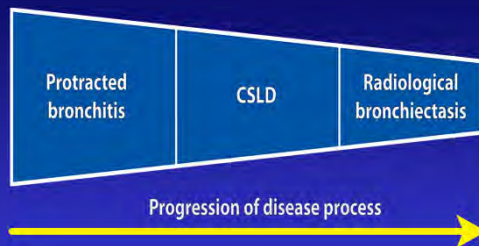
Results

- CXR 63% abnl – most peribronchial thickening
- Spirometry (>6 y/o)–12% abnormal–1 with reversible airway obstruction
- Bronchoscopy–90% macroscopic abnormal
57/95 bronchitis
36/95 malacia
- BAL cell count–68% abnormal (most neutrophilia; 3% eosinophilia)
- C&S *H. flu* 47%, *M. cat* 26%, *S. pneumo* 35%
- Lab
3 IgA deficiency
3 IgG2 deficiency
3 IgE > 1000 IU/mL
3 single Δ F508 CF gene mutation
Sweat cl normal
pHmetry 17% abnl

Marchant, Chest 2006

Malacia in PBB

1. Marchant, Chang 2004 -- 33% tracheo or bronchomalacia (5% bronchiectasis)
2. Douros, 2011 -- no mention
3. Zgherea, 2012 -- 30% (<3 y/o)
4. Kompare, Weinberger, 2012 -- 74%
5. DeBaets, 2012 -- 46%



Using the pathophysiological model, protracted bacterial bronchitis (PBB), chronic suppurative lung disease (CSLD) and radiological bronchiectasis likely represents different ends of a spectrum. This is however speculative and yet to be confirmed. Untreated, it is likely that some (but not all) children with PBB will progress to develop CSLD.

Immune Evaluation in PBB

Marchant, Chang *CHEST* 2006

108 children median age 2.6 yrs.

- 3 IgA deficiency
- 3 IgG₂ deficiency
- 3 single Δ F508 (sweat chloride normal)

Marchant, Chang *Pediatr Pulm* 2008

100 children median age 2.58 yrs.

Airway neutrophil and endobronchial infection -- Innate immune activation defect?

\uparrow BAL -- IL8, active MMP-9, TLR-2 & 4 mRNA expression

Immune Evaluation in PBB

Lim, *AJDC* February 2012

Retrospective review — all child with chronic wet cough (>8 wks) at Pulm Clinic (UK) over 12 mo

96 children — all normal IgG, neg sweat chloride

24/96 (>2 y/o) — Pneumovax II

-14/24 abnormal response — specific ab deficiency (Paris, Sorenson, 2007)

-All nl response to T dependent antigens — tetanus, and/or H. flu type B

-5/24 given Prevnar — all normal response

Conditions Associated with Chronic Cough



Upper Airway Cough Syndrome (Postnasal Drip Syndrome)

- most common cause of chronic cough (41% Irwin, 1990)
- stimulation of afferent limb of cough reflex in upper respiratory tract
- causes:
 - allergic rhinitis
 - nonallergic rhinitis
 - vasomotor rhinitis
 - postinfectious (postviral) rhinitis
 - environmental irritant rhinitis
 - chronic bacterial sinusitis

CVA in Children

- Uncommon cause of chronic cough in studies by Chang at al. Asthma-like conditions found in only 4% of children in Marchant cohort.

“ children with asthma can certainly present with cough alone, but in most children cough in the absence of wheeze and/or dyspnea is rarely asthma.”
Marchant, Chest 2006; 129:1132-41

- Over-diagnosis and over-treatment of asthma in children with chronic cough—Chang.
- In children with asthma who cough, multiple studies showing no correlation between cough frequency/severity and asthma severity (wheezing/sx, airway caliber (FEV1), airway reactivity)
van Asperen, Pediatr Resp Rev 2008; 7:26-30

Use of eNO to predict ICS response in chronic cough

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	+LR	-LR
eNO > 35 ppb	95	80	88	91	4.9	0.07
eNO > 38 ppb	90	85	90	85	5.8	0.12
MCT	66	46	64	48	1.2	0.74

Hahn Mayo Clin Proc 2007

GERD and Chronic Cough (Children)

- Prospective study- 3% GERD (6% > 10 yr). Marchant, 2006
“in contrast w/ adults, little convincing evidence GERD cause of isolated chronic cough in children.” Chang ACCP 2006
- 150 children (mean age 8.2 yrs) w/ chronic cough and GERD sx no assoc of cough with esophagitis by endoscopy . Chang BMC Pediatrics 2006
- Few studies have shown benefit of PPI tx in children w/ GERD and chronic cough (or asthma). Chang Cochrane Reviews, 2006
- 87 children w/ asthma and cough (mean age 7 yrs) not on GERD tx; combined pH and impedance monitoring--38% of cough episodes occurred w/in 2 min of reflux event; equal proportion acid, weak acid, non-acid.
Mehta D. Nemours Childrens Clinic NASPHAN 2006.

Post-viral Cough—Post-infectious Cough

- Very common cause of nonspecific cough
- More common in children vs. adults.
Corraro, Ped Ann 1996; 25:162-8
- Dry cough; due to increased cough receptor sensitivity
- Lasts up to eight weeks by definition (? pertussis)
- Is not CVA
 - No response to beta agonist
 - Response to ICS only if increased ↑ AHR
- Patients may have associated dyspnea, wheeze, reversible airflow obstruction and positive meth PC20 due to transient, viral-induced AHR.
ACCP guidelines 2006

Chang, AIRCCM 1997; 155:1935-39
Chang, Hosp Med 1998; 59:9

Habit Cough Syndrome

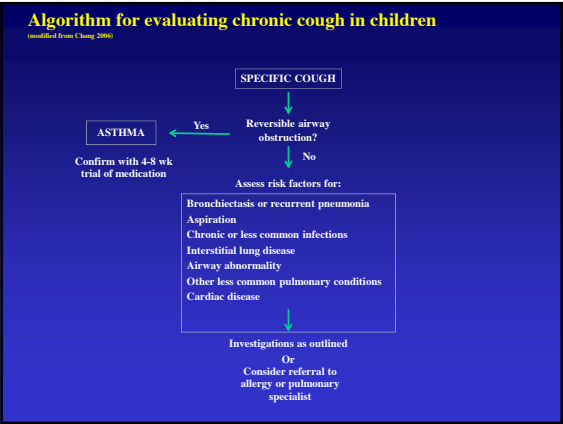
- Dry, repetitive cough; honking character (children)
- Irritative, disruptive-pt unperturbed
- Increases with attention; decreases with involvement in activity and with sleep
- r/o tic disorders, Tourette syndrome
- Marchant 1%, Weinberger 4%; Irwin very rare, overdiagnosed
- Treatment
 - 15 minute suggestion-therapy session Weinberger, Pediatrics 2007
 - self-hypnosis Anbar, J Pediatr 2004
 - behavior modification Vertigan, Gibson, Chronic Respiratory Dis 2007

Algorithm for evaluating chronic cough in children

(modified from Chang 2008)

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graph TD
    A[Sx and signs of respiratory disease?] -- Yes --> D[EVALUATE FOR SPECIFIC COUGH]
    A -- No --> B[CXR, spirometry abnormal?]
    B -- Yes --> D
    B -- No --> C[Is cough characteristic?]
    C -- Yes --> D
    C -- No --> E[NON-SPECIFIC COUGH]
    
    E --> F[1. Watch, wait, review  
• Usually post-infectious  
2. Evaluate  
• Tobacco smoke  
• Environmental exposures  
• Child's activity  
• Parent concerns, expectations  
3. Treat obvious illness]
    F --> G[Review in 1-2 wk]
    G -- Resolving, resolved --> H[ ]
    G -- Persistent cough --> I[Discuss options with parents]
    I --> J[Trial of therapy]
    I --> K[Watch, wait, review]
    J --> L[Dry cough:  
ICS 4-8 wk]
    K --> M[Wet cough:  
Antibiotic 10-21 d]
  
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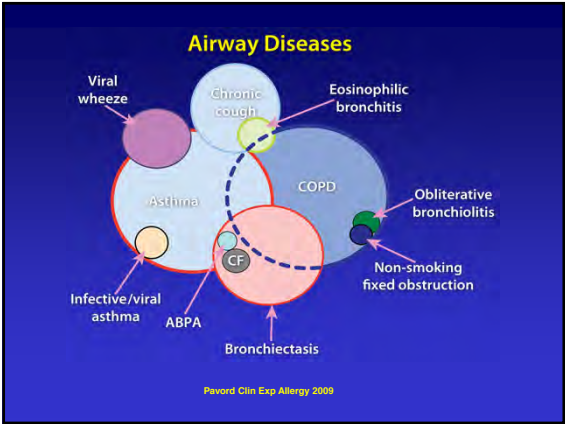
Therapeutic Trials: When to Expect a Response

▪ Smoking Cessation:	up to 4 weeks
▪ ACEI Discontinuation:	up to 4 weeks
▪ Postnasal Drip Syndromes:	up to 2-4 weeks
▪ Asthma:	up to 6-8 weeks
▪ GERD:	up to 8-12 weeks
▪ Eosinophilic Bronchitis:	up to 3-4 weeks

Don't give up too soon!

Chest 1996; 114(2):133a-181a





Other Concepts in Chronic Cough

- Obstructive sleep apnea
 - cough can be the sole manifestation
 - CPAP can effectively resolve cough
 - possible mechanism -upper airway inflammation from epithelial injury or incr transdiaphragmatic pressure → LES insuff → GERD → cough
- Chronic tonsillar enlargement--upper airway inflam
- Hypothyroidism
- Vitamin B12 deficiency
- Iron deficiency

Chronic Cough Hypersensitivity Syndrome

1. Chronic cough duration > 2 months
2. Minimal or no sputum production
3. One or more cough reflex triggers (cold air, speech, eating, odors such as perfume)
4. Urge to cough (tickle or itch) located in throat area (laryngeal hypersensitivity)
5. Adverse impact of cough on QOL
6. Positive cough reflex challenge test (capsaicin)
7. Female predominance

Chronic Idiopathic Cough

Post-viral vagal neuropathy (PVVN) - laryngeal sensory neuropathy - Amin, Koufman, Belafsky

- Vagal nerve injury or dysfunction following an antecedent viral illness
- Post-viral neuropathy, i.e. Bell palsy, Guillain-Barré, post-herpetic neuralgia

Laryngeal dysfunction (VCD) in chronic cough - Vertigan, Gibson

- Chronic cough and throat clearing can cause chronic laryngeal irritation, which can predispose the larynx to be hypersensitive to external stimuli and trigger paradoxical vocal cord closure during inspiration (PVCM)
- Treatment- speech therapy

Irritable larynx syndrome - Bucca

- Laryngeal hyperreactivity (LHR) measurable via histamine inhalation challenge (PVCM)

Chronic Idiopathic Cough

Medical Treatment

- Pregabalin (Lyrica) - GABA analog-- release of neurotransmitters
75 mg b.i.d. ; over three to four weeks to 150 mg b.i.d. (fibromyalgia dose)
Somnolence, dry mouth, blurred vision, dizziness.
- Gabapentin (Neurontin)--? Interact with GABA receptors
100 mg q.d.--100 t.i.d.--300 t.i.d. (slow increase over four weeks)
; Similar side effects as Pregabalin.
- Baclofen - weak GABA analog; decreased release of neurotransmitters
; LES pressure (J. TLESs)
10 mg q.d. x 1 week, b.i.d. x 1 week, t.i.d.
- Amitriptyline - TCA with sedative properties; ; serotonin, NE
FDA approved - depression; used for atypical facial pain, IBS, pain/postherpetic neuralgia
10-20 mg q.h.s.
- Duloxetine (Cymbalta) - also has anxiolytic effect and may interrupt neurotransmitters
Start 30-60 mg/day
- Lidocaine 2-4% solution without ept. Nebulize 2 mL b.i.d.-q.i.d. with or without albuterol
May be irritating to lower airways.
Laryngeal anesthesia--; aspiration
- TRP antagonist
